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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/961,086	ROSS ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *16 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *5-7 and 38-54* is/are pending in the application.

4a) Of the above claim(s) *39,40,45-47 and 52-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *5-7, 38, 41-44, 48-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. The Election filed April 16, 2007 in response to the Restriction requirement mailed March 27, 2007 is acknowledged and has been entered. Claims 5-7, 38, 41-44, 48-51 are currently being examined.

2. Applicant's election with traverse of the species, antibody that binds to a polypeptide consisting of SEQ ID NO:1, positions 79-86 in the paper submitted on April 16, 2007 is acknowledged. The traversal is on the ground(s) that the restricted amino acid sequences are very closely related and are portions of the same polypeptide, SEQ ID NO:1. It appears that Applicant is traversing on the grounds that the examination of all of the claimed antibodies would not impose a serious burden on the examiner. The argument has been considered but has not been found persuasive because, contrary to Applicant's arguments, the amino acid sequences of the peptides to which the antibodies bind are not closely related as they each represent a different epitope with a different structure and function. Although each of the peptides is obtained from SEQ ID NO:1, separate searches in the sequence databases is required for each of these peptides and the peptides are not obvious one over the other. Different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

3. Examiner appreciates Applicant's question and request for clarification drawn to the disclosure, on the Office Action Summary mailed October 13, 2006, that claims 39 and 40 are allowed, wherein Applicant understands that these two claims are in fact withdrawn from consideration. Upon review and consideration it is clear that claims 39-40 are not allowed and in fact are withdrawn from consideration and that because of an unintentional typographical error, Examiner placed claims 39-40 on the line below the line reserved for claims that are

withdrawn from consideration, that is, the line reserved for allowed claims. Examiner apologizes for any inconvenience.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. The following rejections are being maintained:

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 5, 7, 38 remain rejected under 35 USC 103 for the reasons previously set forth in the paper mailed October 13, 2006, Section 5, pages 2-8.

Applicant traverses the rejection for the reasons of record. The previous arguments were considered and not found persuasive for the reasons of record.

Applicant argues that new claims 41-53 recite antibodies that bind particular domains of the polypeptide of SEQ ID NO;1, thus, new claims 41-44 and 48-51 are drawn to antibodies that bind to specific portions of SEQ ID NO;1. Further claims 48-51 recite antibodies that bind to particular domains of the polypeptide of SEQ ID NO;1 and that permit intracellular accumulation of doxorubicin in MCf-7 cells that express the polypeptide of SEQ ID NO:1 and the prior art of record does not read on any of these claims.

The arguments have been considered but have not been found persuasive because Applicant is arguing limitations not recited in the claims as currently constituted as none of claims 5, 7 or 38 recite the newly added claim limitations.

Maintained and New Grounds of Rejection

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 38 remains rejected and newly added claims 44 and 51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons previously set forth in the paper mailed October 13, 2006, Section 6, pages 8-10.

Applicant argues that an intended use for the pharmaceutical composition is not recited in claim 38.

The argument has been considered but has not been found persuasive because as previously set forth, inherent in the recitation of the term "pharmaceutical composition" is the in vivo use thereof for the treatment of disease. Thus, the claims read on the intended use of treatment of disease.

Applicant states that Examiner appears to argue that evidence of efficacy in treating patients is necessary to enable the invention as claimed and argues that this is an improper requirement since patentability does not require establishment of clinical efficacy for a pharmaceutical composition.

The argument has been considered but has not been found persuasive because it appears that Applicant is misinterpreting Examiner's arguments. Examiner does not argue that evidence of efficacy in treating patients is necessary to enable the invention as claimed, rather Examiner points to the unpredictability of the cancer therapy arts and to the unpredictability of cancer drug discovery. Given that the specification provides no objective evidence that the claimed invention can be used as a pharmaceutical composition with a reasonable expectation of success, given the unpredictability of the cancer therapy art, given that the only teaching in the specification drawn to the use of a pharmaceutical composition is that "it is also an object of the invention to provide a method of reversing the drug resistance of cancer cells by administering BCRP antibodies/a method of enhancing a patient's chemotherapy treatment for breast cancer by administering antibodies to the patient to inhibit BCRP", given that little is known about the invention, that is, that it is an undeveloped art, no one of ordinary skill in the art would believe it more likely than not that the invention will function as claimed, that is as a pharmaceutical composition, or as contemplated in the specification for reversing the drug resistance of cancer cells by administering BCRP antibodies/a method of enhancing a patient's chemotherapy treatment for breast cancer.

Applicant argues that the specification teaches that the antibodies of the invention can be employed to assay for the presence of amount of BCRP in a particular biological sample. The argument has been considered but has not been found persuasive because the claims are drawn to pharmaceutical compositions and inherent in the pharmaceutical composition is the in vivo use thereof for the

treatment of disease. It is clear that the assays disclosed in the specification are drawn to in vitro and not in vivo applications.

Applicant argues that one of skill in the art would readily understand that anti-BCRP antibodies could be used in *in vivo* diagnostic techniques, in addition to the other uses noted by the Examiner. For example, a radiolabeled antibody could be administered to the patient in order to locate and ass BCRP levels in a particular region of the body.

The argument has been considered but has not been found persuasive because a search of the specification as originally filed does not reveal, suggest or contemplate the use of the antibodies for in vivo imaging techniques, does not reveal that BCRP protein is differentially expressed on cancer cells compared to normal controls. Thus contrary to Applicant's arguments, one would not readily understand that anti-BCRP antibodies could be use in *in vivo* diagnostic techniques.

Applicant argues that the skilled artisan would accept that BCRP is a worthwhile target against which a pharmaceutical composition could be developed for use in the treatment of cancer and that the generation of specific antibodies, as well as pharmaceutical formulations is now a routine procedure and would not require undue experimentation.

The argument has been considered but has not been found persuasive because for the reasons of record, no one would believe it more likely than not that the claimed invention would function as claimed, that is as a pharmaceutical composition. Although the generation of specific antibodies and the production of pharmaceutical formulations is routine, the development of pharmaceutical compositions for the treatment of cancer is not.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

10. Claims 41-44, 48-51 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitations of an antibody that binds to a polypeptide comprising an amino acid sequence selected from position 79 to 86 of SEQ ID NO:1/pharmaceutical composition comprising an antibody that bind to a polypeptide comprising an amino acid sequence selected from position 79 to 86/wherein said antibody permits accumulation of daunorubicin in MCF-7 cells expressing a polypeptide having the amino acid sequence of SEQ ID NO:1 has no clear support in the specification and the claims as originally filed. Applicant points to support for the newly added claims at page 9, lines 17-19, page 10, lines 9-10, Figures 2A, 4B and 4D, and in particular for the new domains in Fig 2A. The suggested support has been considered but has not been found persuasive because a review of page 9, lines 17-19 reveals support only for "antagonists can be immunoglobulins", a review of page 10, lines 9-10 reveals support only for "A polyclonal antibody capable of binding to BCRP can be prepared by immunizing a mammal with a preparation of BCRP or functional derivative of BCRP", a review of Figure 2A reveals that Fig. 2A is drawn to the deduced amino acid sequence of BCRP with motifs, a review of Figure 4B reveals that Fig. 4B is a graph of Daunorubicin (DNR) accumulation and retention in the pcDNA3 vector control cells and BCRP-transfected clones 6 and 8, a review of Figure 4D reveals that Fig. 4D discloses graphs showing the effect of various chemotherapeutic drugs' concentrations on BCRP-transfected MCF-7 clone 8 cell survival and that none of the suggested support is drawn to antibodies that specifically bind to an amino acid sequence selected from position

79 to 86 of SEQ ID NO:1/pharmaceutical composition comprising an antibody that bind to a polypeptide comprising an amino acid sequence selected from position 79 to 86/wherein said antibody permits accumulation of daunorubicin in MCF-7 cells expressing a polypeptide having the amino acid sequence of SEQ ID NO:1. Further, as drawn to Fig. 2A, which Applicant particularly points to for support of the newly claimed invention, a review of the specification reveals only the following drawn to the Fig. 2A, none of which is drawn to antibodies that specifically bind to a polypeptide comprising an amino acid sequence selected from position 79 to 86 of SEQ ID NO:1/pharmaceutical composition comprising an antibody that binds to a polypeptide comprising an amino acid sequence selected from position 79 to 86/wherein said antibody permits accumulation of daunorubicin in MCF-7 cells expressing a polypeptide having the amino acid sequence of SEQ ID NO:1.

> (1) "FIG. 2A is the deduced amino acid sequence of BCRP with motifs." At paragraph 0020 of the published application.
> (2) "The present invention pertains partially to the BCRP, to fragments of this factor, as well as to functional derivatives, agonists and antagonists, and metabolic breakdown products of this factor. The BCRP amino acid sequence is depicted in SEQ ID No. 1 and FIG. 2A." at paragraph 0037 of the published application.
> (3) "Examination of BCRP structure with GCG programs "PEPPLOT" and "PLOTSTRUCTURE" revealed a relatively hydrophilic amino-terminal domain (amino acids 1-400) that contains the ATP-binding sequence and a relatively hydrophobic carboxy-terminal domain (amino acids 401-655), containing at least three putative transmembrane domains (TM1, TM2, and TM3), and four potential N-glycosylation sites (Glyc) (FIG. 2A)." at paragraph 0074 of the published application." at paragraph 0072 of the published application.
> (4) "[0073] Analysis of the sequence of BCRP with the GCG program "MOTIFS" demonstrated a single Walker "A" ATP/GTP binding region (11)

> at amino acids 80-87 and a phosphopantetheine attachment site at amino acids 213-228 (FIG. 2A)." at paragraph 0073 of the published application. (5) "Examination of BCRP structure with GCG programs "PEPPLOT" and "PLOTSTRUCTURE" revealed a relatively hydrophilic amino-terminal domain (amino acids 1-400) that contains the ATP-binding sequence and a relatively hydrophobic carboxy-terminal domain (amino acids 401-655), containing at least three putative transmembrane domains (TM1, TM2, and TM3), and four potential N-glycosylation sites (Glyc) (FIG. 2A)." at paragraph 0074 of the published application.

The subject matter claimed in claims 41-44, 48-51 broadens the scope of the invention as originally disclosed in the specification.

10. Claims 41-44, 48-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody that binds to residues 79 to 86 of SEQ ID NO:1, does not reasonably provide enablement for antibody that binds to a polypeptide comprising residues 79 to 86 of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are drawn to an isolated antibody that binds to a polypeptide comprising an amino acid sequence selected from position 79 to 86 of SEQ ID NO:1/pharmaceutical composition comprising an antibody that bind to a polypeptide comprising an amino acid sequence selected from position 79 to 86/wherein said antibody permits accumulation of daunorubicin in MCF-7 cells expressing a polypeptide having the amino acid sequence of SEQ ID NO:1.

The specification teaches that Figure 2A discloses the deduced amino acid sequence of BCRP with motifs, wherein the motifs include a Walker A motif (see Description of the Drawings). The specification further teaches at page 10 that

polyclonal antibodies against BCRP can be prepared by immunizing a mammal with a preparation of BCRP of functional derivative thereof and at page 9 that antagonists of BCRP can be immunoglobulins.

One cannot extrapolate the teaching of the specification to the scope of the claims because the claims are drawn to antibody that binds to an unknown and unidentified polypeptide which comprises amino acids 79 to 86 of SEQ ID NO:1 but which does not require that the antibody bind to amino acids 79 to 86 of SEQ ID NO:1.

In particular, the claims are drawn to an antibody that binds to a polypeptide comprising amino acid residues 79 to 86 of SEQ ID NO:1 but which does not require that the antibody bind to amino acids 79 to 86 of SEQ ID NO:1. Thus the claims are claiming an antibody that binds to the unknown portion of the claimed polypeptide, that is the portion of the polypeptide that is not amino acids 79 to 86 of SEQ ID NO:1. The following teaching of the court as set out in Noelle also clearly applies to the instant claimed invention. The court found that "Noelle did not provide sufficient support for the claims to the human CD40CR antibody in his '480 application because Noelle failed to disclose the structural elements of human CD40CR antibody or antigen in his earlier '799 application. Noelle argues that because antibodies are defined by their binding affinity to antigens, not their physical structure, he sufficiently described human CD40CR antibody by stating that it binds to human CD40CR antigen. Noelle cites Enzo Biochem II for this proposition. This argument fails, however, because Noelle did not sufficiently describe the human CD40CR antigen at the time of the filing of the '799 patent application. In fact, Noelle only described the mouse antigen when he claimed the mouse, human, and genus forms of CD40CR antibodies by citing to the ATCC

number of the hybridoma secreting the mouse CD40CR antibody. If Noelle had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the "fully characterized" antigen. Noelle did not describe human CD40CR antigen. Therefore, Noelle attempted to define an unknown by its binding affinity to another unknown. As a result, Noelle's claims to human forms of CD40CR antibody found in his '480 application cannot gain the benefit of the earlier filing date of his '799 patent application. Moreover, Noelle cannot claim the genus form of CD40CR antibody by simply describing mouse CD40CR antigen". *Randolph J. Noelle v Seth Lederman, Leonard Chess and Michael J. Yellin* (CAFC, 02-1187, 1/20/2004). Identical to Noelle, the instant claims are attempting to define an unknown antibody by its binding affinity to another unknown, that is the portion of the polypeptide "comprising" that is not amino acids 79 to 86 of SEQ ID NO:1, Thus, one of ordinary skill in the art would not known how to use the claimed invention.

Claim Rejections - 35 USC § 103

11. Claims41, 43, 44, 48, 50, 51 are rejected under 35 USC 103 as being unpatentable over Gibbons B.H. et al (Mol. Biol. Cell 5:57-70, 1994, see sequence comparison below) and further in view of Harlow et al, of record.

It is noted Roitt et al, or record specifically teach that when the determinants of antigen A are shared by another antigen, B, then antibodies that bind to those determinants in A will also react with B. This phenomenon is termed cross-reactivity (see Fig 6.8 on page 6.4 and p. 6.5, para 1), thus antibody to an epitope that "binds specifically" to a particular antigen will also bind specifically to other proteins that share the same epitope. Further, Herbert et al, of record, specifically teach that an epitope is the region on an antigen molecule to which

antibody specifically binds. Antibodies bind in a more or less exact three dimensional fit with an epitope (p. 58), thus the exact constitution of the amino acids forming the epitope is not critical as long as their three-dimensional fit produces an epitope to which the antibody will bind. Given that it is understood in the art that conservative substitutions are amino acid replacements that preserve the structure and functional properties of proteins, it would be expected that any protein that comprises amino acids 79 to 86 or conservative substitutions thereof would cross react with antibodies that bind to said amino acid residues on a different molecule.

The claims are drawn to an antibody which binds specifically to a polypeptide comprising amino acids 79 to 86 of SEQ ID NO:1, polyclonal antibody.

Gibbons et al teach a polypeptide comprising amino acids 80 to 86, wherein the amino acid preceding said amino acids is a conservative substitution, of amino acid 79 of SEQ ID NO:1.

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AC   Q27807;
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DT   18-APR-2006, entry version 27.
DE   Dynein heavy chain isotype 5A (EC 3.6.1.3) (Fragment).
GN   Name=DYH5A;
OS   Tripneustes gratilla (Hawaian sea urchin).
OC   Eukaryota; Metazoa; Echinodermata; Eleutherozoa; Echinozoa;
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RX   MEDLINE=94243035; PubMed=8186465;
RA   Gibbons B.H., Asai D.J., Tang W.J., Hays T.S., Gibbons I.R.;
RT   "Phylogeny and expression of axonemal and cytoplasmic dynein genes in
RT   sea urchins.";
RL   Mol. Biol. Cell 5:57-70(1994).
CC   ---------------------------------------------------------------------
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CC   Copyrighted by the UniProt Consortium, see http://www.uniprot.org/terms
CC   Distributed under the Creative Commons Attribution-NoDerivs License
CC   ----------------------------------------------------------------------
DR   EMBL; U03977; AAA63591.1; -; mRNA.
DR   PIR; T30879; T30879.
DR   GO; GO:0005524; F:ATP binding; IEA.
DR   GO; GO:0042624; F:ATPase activity, uncoupled; IEA.
DR   GO; GO:0016787; F:hydrolase activity; IEA.
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  Best Local Similarity   87.5%;  Pred. No. 5.6e+02;
  Matches    7;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 LGPTGGGK 8
              :|||||||
Db        321 VGPTGGGK 328
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The reference teaches as set forth above but does not teach polyclonal antibody that binds to amino acids 79 to 86 of SEQ ID NO:I.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have produced polyclonal antibodies to the polypeptide of Gibbons et al because the Board of Patent Appeals and interferences has taken the position that once an antigen has been isolated, the manufacture of antibodies against it is prima facie obvious. See Ex parte Ehrlich, 3 USPQ 2d 1011 (PTO Bd. Pat. APP. & Int. 1987), Ex parte Sugimoto, 14 USPQ 2d 1312 (PTO Bd. Pat. App. & Int. 1990). Given that the art understands that antibodies bind in a more or less three dimensional fit, given that the art recognizes that conservative substitutions of amino acids would be expected to maintain structure due to similarity of conservative substitution, given that polyclonal antibodies bind to multiple sites on a protein, it would be expected that at least a subset of the antibodies produced against the polypeptide of Gibbons et al would

bind to the amino acids that are identical to, or conservatively substituted for amino acids 79 to 86 of SEQ ID NO:1. Further, it would be expected that these antibodies would bind to amino acids 79 to 86 of any polypeptide comprising said amino acids because it is known in the art that specific binding is drawn to common epitopes.

12. Claim 6 is allowed.

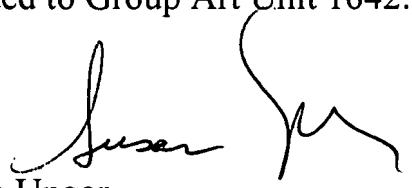
13. Applicant's amendment necessitated the new grounds of rejection. Thus, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley, can be reached at 571-272-0898. The fax phone number for this Art Unit is (571) 273-8300.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.



Susan Ungar
Primary Patent Examiner
June 27, 2007